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Inhibition of T cell signaling by immunophilin-ligand complexes correlates with loss of calcineurin phosphatase activity.

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Calcineurin, a Ca2+, calmodulin-dependent protein phosphatase, was recently found to bind with high affinity to two different immunosuppressant binding proteins (immunophilins) with absolute dependence on the presence of the immunosuppressants FK506 or cyclosporin A (CsA) [Liu et al. (1991) Cell 66, 807-815]. The binding affinities of the immunophilin-drug complexes toward calcineurin and the stoichiometry of the resultant multimeric complexes have now been determined, and structural elements of FK506, CsA, and calcineurin that are critical for mediating their interactions have been identified. Analogues of FK506 (FK520, FK523, 15-O-demethyl-FK520) and CsA (MeBm2t1-CsA and MeAla6-CsA) whose affinities for their cognate immunophilins do not correlate with their immunosuppressive activities have been prepared and evaluated in biochemical and cellular assays. We demonstrate a strong correlation between the ability of these analogues, when bound to their immunophilins, to inhibit the phosphatase activity of calcineurin and their ability to inhibit transcriptional activation by NF-AT, a T cell specific transcription factor that regulates IL-2 gene synthesis in human T cells. In addition, FKBP-FK506 and CyP-CsA do not inhibit members of the PP1, PP2A, and PP2C classes of serine/threonine phosphatases. These data suggest that calcineurin is the relevant cellular target of these immunosuppressive agents and is involved in Ca(2+)-dependent signal transduction pathways in, among others, T cells and mast cells.

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